REMARKS

In response to the Non-Final Office Action mailed March 19, 2010, and having a period for response set to expire on June 19, 2010, Applicant respectfully requests that the Examiner favorably consider the following remarks.

Amendments to the Claims

With the present submission, no claims have been amended. Claims 1-31 are pending. Claims 2, 8-12, 15, 16, 24-30, and 32 were previously withdrawn as being drawn to a non-elected invention. Accordingly, claims 1, 3-7, 13, 14, 17-23, and 31 are currently under consideration.

Rejections under 35 U.S.C. § 112

Claims 1, 3-7, 13, 14, 17-23 and 31 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because "[i]t is unclear how each strand can have a maximum length of 38 nucleotides but also comprise at least 48 nucleotides of XZ or YZ". (Office action, pages 2-3) Applicant respectfully traverses the rejection on the basis that, contrary to the Office's assertion, none of the instant claims require sequence XZ or YZ to be at least 48 nucleotides. The Office appears to mistake the *absolute length requirements* of sequences XZX' and YZY' (having length between 24 and 38 nucleotides) with the *permitted ranges* of sequence Z (having length from 1 to 24 nucleotides) and sequences X and Y (each having length from 1 to 21 nucleotides). Claim 1 therefore allows for various combinations of length for portions X, Y, and Z within *permissive ranges* so long as the *overall length requirement* of XZX' and YXY is met. Applicant respectfully requests withdrawal of the rejection.

Rejections under 35 U.S.C. § 103(a)

Claims 1, 3-7, 13, 14, 17-23 and 31 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious in view of Turner *et al.* (US 2004/0053876), Tuschl *et al.,* (US 2004/0259247), Rana *et al.,* (US 2005/0020521), Parrish *et al.,* (Molecular Cell, Vol. 6, pages 1077-1087, 2000), Pieken *et al.,* (Science, 1991, 253:314-317), Sullenger *et al.,* (US 2003/0083294), Matulic-Adamic *et al.,* (US 5,998,203), Braasch *et al.* (Biochemistry, 2002 Vol. 41:4503-4510), as evidenced by Caplen (Expert Opinion Biol. Ther., 2003, 3:575-586), Anderson *et al.,* (Oligonucleotides 2003) and Leirdal *et al.,* (Biochem and Biophys 2002). Applicant respectfully traverses the rejection with respect to claims 1, 3-7, 13, 14, 17-23, and 31 because each of the cited references, Turner *et al.*, Tuschl *et al.,* Rana *et al.,* Parrish *et al.*, Pieken *et al.*, Sullenger *et al.*, Matulic-Adamic *et al.,* Braasch *et al.*, Caplen *et al.*, Anderson *et al.,* and Leirdal *et al.,* alone or in combination, fail to teach or suggest all of the features of the instant invention. Applicant respectfully maintains that the missing features are not fairly suggested or taught by the cited references or the general knowledge in the prior art. Furthermore, based on the lack of guidance offered by the prior art, Applicant respectfully maintains that one of skill in the art would not have any reasonable expectation of success in arriving at or practicing the instant invention. Accordingly, Applicant respectfully requests withdrawal of the rejection.

The controlling jurisprudence

When determining whether a claim is obvious, an examiner must first make "a searching comparison of the claimed invention – *including all its limitations* – with the teaching of the prior art." *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis added). Thus, "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (*citing In re Royka*, 490 F.2d 981, 985 (CCPA 1974)). The Supreme Court's decision in *KSR International Co. v. Teleflex Inc.,* 127 S. Ct. 1727 (2007) does not change the requirement of this first step in an obviousness determination as previously promulgated by the Federal Circuit Court of Appeals (CAFC): i.e., ascertaining that each and every claim limitation has been disclosed or suggested by the prior art. This first step was again affirmed by the CAFC in *Abbott Laboratories v. Sandoz,* 2007-1300, *16 (Fed. Cir.

October 21, 2008), where the district court's interpretation of the *KSR* opinion in this respect was said to be correct:

> *The KSR opinion only focused on the Federal Circuit's strict use of the TSM [teaching, suggestion, motivation] test in performing the obviousness analysis; it did not mention or affect the requirement that* ***each and every claim limitation must be found present*** *in the combination of the prior art references before the analysis proceeds.*

Id. at *16-*17 (*emphasis added*).

The failure of an asserted combination to reveal each and every limitation of a claim therefore remains fatal to an obviousness rejection under 35 U.S.C. § 103. As such, the asserted combination of Turner *et al.*, Tuschl *et al.,* Rana *et al.,* Parrish *et al.*, Pieken *et al.*, Sullenger *et al.*, Matulic-Adamic *et al.,* Braasch *et al.*, Caplen *et al.*, Anderson *et al.,* and Leirdal *et al.,* must teach or reasonably suggest to one of skill in the art *each and every claim limitation* to support a *prima facie* finding of obviousness. Applicant maintains that the Office has not provided any references that, alone or in combination, teach or suggest the limitations of the invention as described and claimed, and has therefore not established any *prima facie* showing of obviousness for the invention as is presently claimed using the asserted combination of prior art references.

The claim limitations not taught or suggested by the prior art

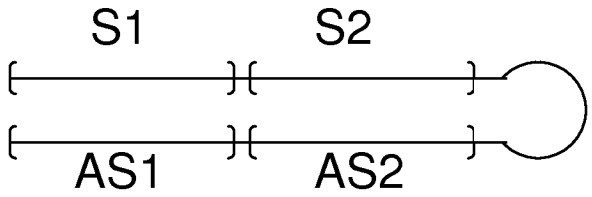
The cited art, alone or in combination, fails to teach the present limitations of claim 1 and any claims dependent thereon. Specifically, the claimed multifunctional siNA molecules have the formula:

5'-p-X Z X'-3'
3'-Y'Z Y-p-5'

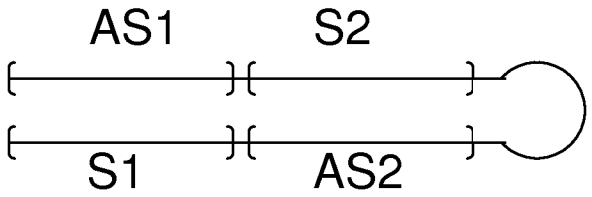
wherein each 5'-p-XZX'-3' and 5'-p-YZY'-3' independently comprise an oligonucleotide of length between 24 and 38 nucleotides, XZ comprises a nucleic acid sequence that is complementary to a first target nucleic acid sequence, YZ comprises an oligonucleotide comprising nucleic acid sequence that is complementary to a second target nucleic acid

sequence, Z comprises nucleotide sequence of length 1 to 24 nucleotides that is complementary between regions XZ and YZ, X comprises nucleotide sequence of length 1 to 21 nucleotides that is complementary to nucleotide sequence present in region Y', Y comprises nucleotide sequence of length 1 to 21 nucleotides that is complementary to nucleotide sequence present in region X', p comprises a terminal phosphate group that can independently be present or absent, and wherein each said XZ and said YZ are independently of length sufficient to stably interact with said first and said second target nucleic acid sequence, respectively, or a portion thereof.

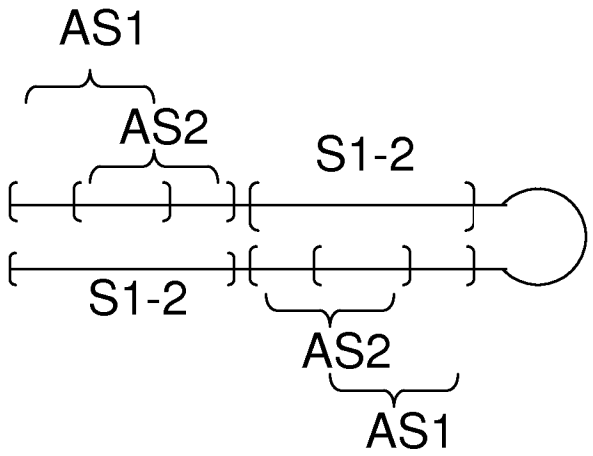
The Turner *et al.* reference speculates that it might be possible to target more than one RNA with a single hairpin siRNA molecule and proposes several hairpin siRNA structures that may have this capability, none of which comprises the features of the presently claimed siNA molecules. For example, Turner et al. suggests a hairpin siRNA comprising at least two different non-overlapping antisense sequences, wherein each antisense sequence is from about 18 to about 29 nucleotides long. The non-overlapping antisense sequences can be adjacent to each other on one strand (as shown below).



Alternatively, the non-overlapping antisense sequences can be on separate strands of the hairpin siRNA (shown below). As depicted, Turner *et al.* envisions a single-stranded hairpin siRNA with an antisense sequence 1 on one strand and an antisense sequence 2 on another strand, wherein the antisense sequences are complementary with corresponding sense sequences on the opposite strands but not with each other.



Turner *et al.* further contemplates that "any of the antisense sequences may also comprise a set of two overlapping antisense sequences". A schematic drawing of this structure is shown:



As depicted in each of the schematics drawings, Turner *et al.* envisions entirely different siRNA structures from the presently claimed multifunctional siNA molecules. Specifically, the Turner *et al.* molecules are single stranded hairpin siRNA molecules rather than double stranded siNA molecules having two separate oligonucleotide strands. Furthermore, the Turner *et al.* hairpin siRNA molecules do not have different antisense sequences on separate oligonucleotide strands that are at least partially complementary to one another. Importantly, Turner *et al.* does not disclose the "Z" portions of the instantly claimed multifunctional siNA molecules having sequences 5'-p-XZX'-3' and 5'-p-YZY'-3' with XZ and YZ being separate and distinct antisense regions with complementarity to different target nucleic acid molecules. Thus, Turner *et al.* fails to show or suggest all of the limitations of the presently claimed siNA molecules.

None of the other cited references cure the deficiencies of Turner *et al.* with respect to the missing element "Z". Leirdal *et al.* only describe a bispecific motif formed by two co-joined short hairpin RNA molecules having a single continuous sequence. Anderson *et al.* only describe bispecific siRNA molecules containing an 8-nucleotide intervening spacer that was shown to be cleaved in vitro to yield two monospecific siRNAs against different targets. Tuschl *et al.,* Rana *et al.,* Parrish *et al.*, Pieken *et al.*, Sullenger *et al.*, Matulic-Adamic *et al.,* Braasch *et al.*, and Caplen *et al.* do nothing to teach or suggest bifunctional or multifunctional constructs at

all, and certainly do not remedy the deficiencies of Turner *et al.,* Leirdal *et al.,* and Anderson *et al.* with respect to the missing element "Z".

The Office has not provided any *prima facie* showing of obviousness

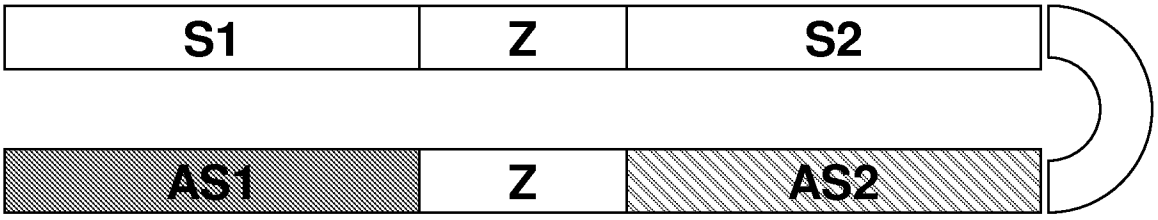
The Office has not provided any *prima facie* showing of obviousness for at least two reasons. First, as addressed above, the Office has not provided any references or other evidence that, in aggregate, either explicitly or implicitly, teaches each of the limitations of the instant invention. Second, the Office has failed to provide any evidence that one of skill in the art would have any reasonable expectation of success in arriving at or practicing the presently claimed invention.

Prior art does not teach all claim limitations

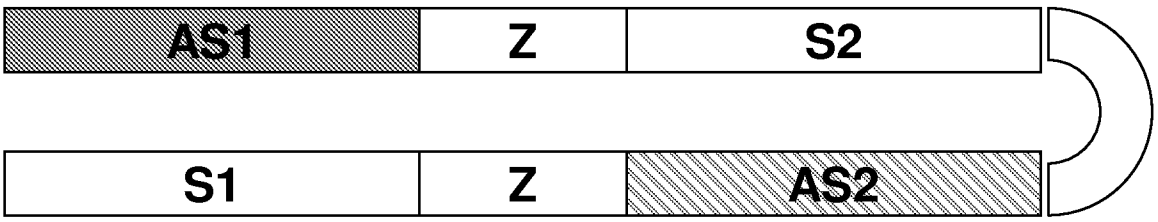
The Office asserts that "Turner *et al.* teach siRNA molecules capable of inhibiting the expression of target genes and teach a multi-target siRNA comprising at least two antisense regions that are complementary to different target genes and that are complementary to sense regions on the opposite strands (sections X' and Y' of the instantly claimed molecule), and wherein the antisense that is adjacent to a sense strand can be a contiguous strand or separated by one to several nucleotides (see at least paragraph 218-219)." Office action, page 4. Furthermore, the Office asserts that "[t]he claimed siNA molecule recites Z comprises nucleotides that are complementary between the antisense regions. Turner *et al.* teach the antisense regions can be separated by one to several nucleotides and these nucleotides would be complementary to the nucleotides on the opposite strands and could therefore bind a target molecule." Office action, page 8.

Applicant respectfully maintains that the Office has not provided any evidence of the constructs as claimed having a configuration comprising sequences XZX' and YZY' wherein the "Z" portion has overlapping complementarity between the two antisense regions XZ and YZ, and that these missing features are not taught or suggested by any of the cited art, alone or in aggregate. Contrary to the Office's assertion, the Z portion of the claimed invention does not comprise "nucleotides that are complementary between the antisense regions", i.e. a spacer or

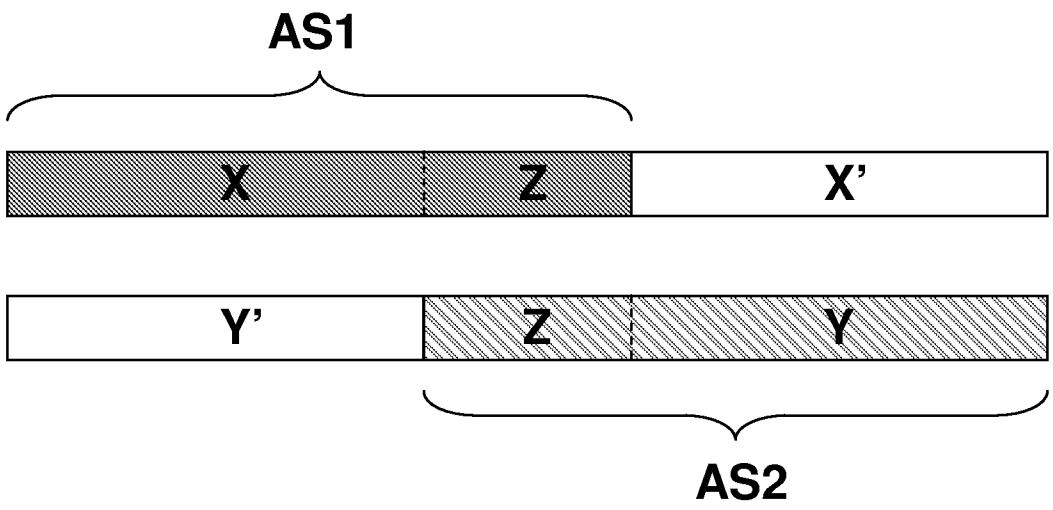
linker, but is rather a portion of shared complementarity of each XZ and YZ antisense region. With respect to the hairpin molecules of Turner *et al.,* Turner specifically teaches that "[t]he antisense sequences may be adjacent to each other in one strand of an siRNA; in these embodiments, the antisense sequences may be contiguous, *or they may be separated from each other by from about one to several nucleotides*." (see paragraph [0218], page 21, *emphasis added*) This alleged "Z" region of Turner *et al.* is clearly a spacer region between the antisense regions and is not a region of shared complementarity between the two antisense regions as is shown diagrammatically below:



Alternately, Turner specifically teaches that "[i]n embodiments where one antisense sequence is adjacent to a sense sequence for a second or different antisense sequence, the two adjacent sequences may be contiguous, *or they may be separated by from about one to several nucleotides*." (see paragraph [0218], page 22, *emphasis added*) This alleged "Z" region of Turner *et al.* is clearly a spacer region between the sense and antisense regions and is not a region of shared complementarity between the two antisense regions as is shown diagrammatically below:



Neither of these arrangements teach or suggest the constructs as claimed having a configuration comprising sequences XZX' and YZY' wherein the "Z" portion has overlapping complementarity between the two antisense regions (as opposed to being a spacer region as required by Turner *et al.*) as shown diagrammatically below:



The claimed multifunctional siNA molecules having a configuration comprising sequences XZX' and YZY' wherein the "Z" portion has overlapping complementarity between the two antisense regions represents a feature that is not taught or suggested by Turner *et al.* or any of the other cited references. The Office has mistakenly characterized the teachings of Turner *et al.* in alleging that the spacer portion of the Turner *et al.* molecules are equivalent to the claimed "Z" portion of the instantly claimed invention, which is a region of overlapping complementarity between the two antisense regions XZ and YZ of each separate XZX' and YZY' strand. Simply stated, the compositions taught by Turner *et al.*, Tuschl *et al.,* Rana *et al.,* Parrish *et al.*, Pieken *et al.*, Sullenger *et al.* (US 2003/0083294); Matulic-Adamic *et al.,* Braasch *et al.*, Caplen *et al.*, Anderson *et al.,* and Leirdal *et al.,* alone or in combination, fail to teach or suggest all of the features of the instantly claimed invention.

"Obvious to try" inquiry fails in any showing of obviousness

The Office alleges that "given that Turner et al. teach various configurations of a multi-target RNAi molecule, the instant invention would have been obvious to the skilled artisan." Office action, page 9. The Office appears to rely on hindsight in arguing that the claimed molecules having specific configurations are disclosed by the combination of 11 references, i.e. Turner *et al.*, Tuschl *et al.,* Rana *et al.,* Parrish *et al.*, Pieken *et al.*, Sullenger *et al.*, Matulic-Adamic *et al.,* Braasch *et al.*, Caplen *et al.*, Anderson *et al.,* and Leirdal *et al.* The Office is

essentially arguing that the present invention would be "obvious to try" and is therefore *prima facie* obvious. Applicant respectfully traverses. The Federal Circuit has clarified the standard for a finding of obviousness based on "obvious to try" in *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009). While acknowledging that, as stated by the U.S. Supreme Court in *KSR International Co. v Teleflex Inc.,* a skilled artisan, when motivated by an unmet need, can look to combine elements within the scope of the prior art, it would be improper to hold a claim obvious when:

> *what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result; where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful*

or

> *what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.*

To hold a claim obvious under these situations would be, according to the Federal Circuit, "succumb[ing] to hindsight claims of obviousness" and erroneous. *Id.*

"In such circumstances, where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness." *Kubin,* at 1359.

Here, because the cited references provide no guidance, teaching, or suggestion of the specific configuration of the multifunctional siNA molecules as claimed, one of skill in the art would not have any reasonable expectation of success in arriving at or practicing the presently claimed invention. Any assertion to the contrary must therefore arise from inappropriate hindsight in view of Applicant's own disclosure.

In view of the foregoing, Applicant respectfully submits the pending claims are in condition for allowance but for the residual provisional double-patenting issue. If the Examiner believes a telephone conference would expedite prosecution of this application, she is urged to telephone the undersigned at the telephone number below.

Respectfully submitted,

Date: June 4, 2010

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